Application No.:

REMARKS

The attached amendments are to correct obvious software errors in the original filed PCT application.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made**."

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

Reg. # 37,004

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Date: May 16, 2001
AJZ/tal:k:\sch\1799\Preliminary Amendment-2

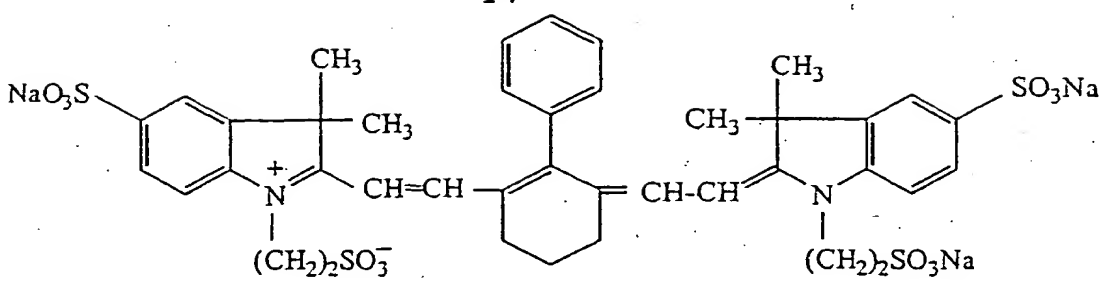
Application No.:

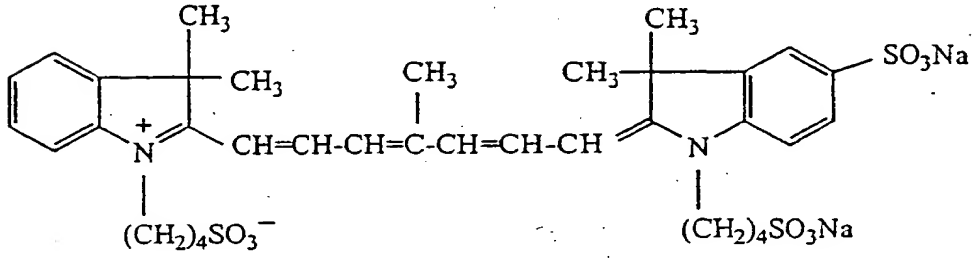
VERSION WITH MARKINGS TO SHOW CHANGES MADE

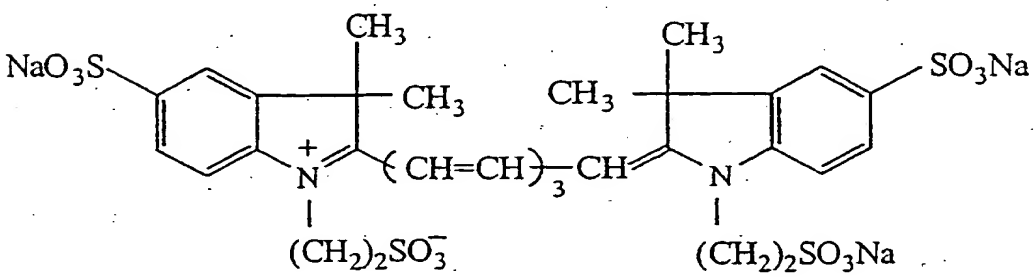
IN THE SPECIFICATION

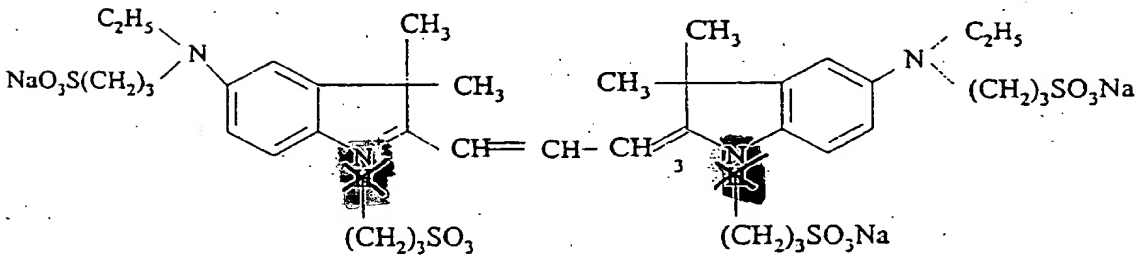
Please see the attached pages 14, 15, 23, 49, 52, 56, 71, 72, 74, 98 and 106 with markings to show the changes.

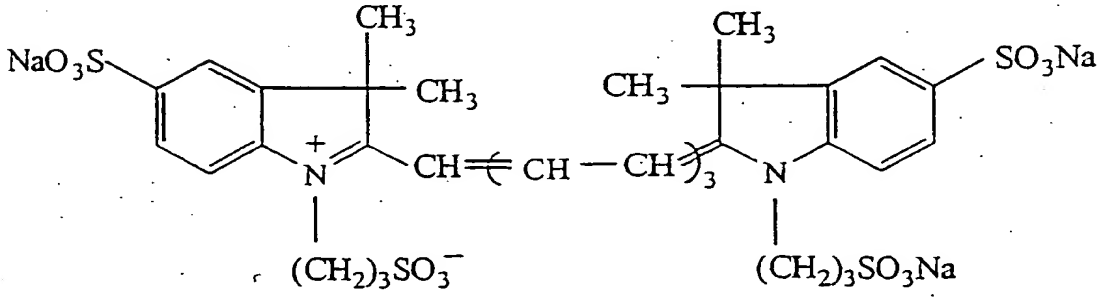
Also attached new pages 14, 15, 23, 49, 52, 56, 71, 72, 74, 98 and 106 with changes made.

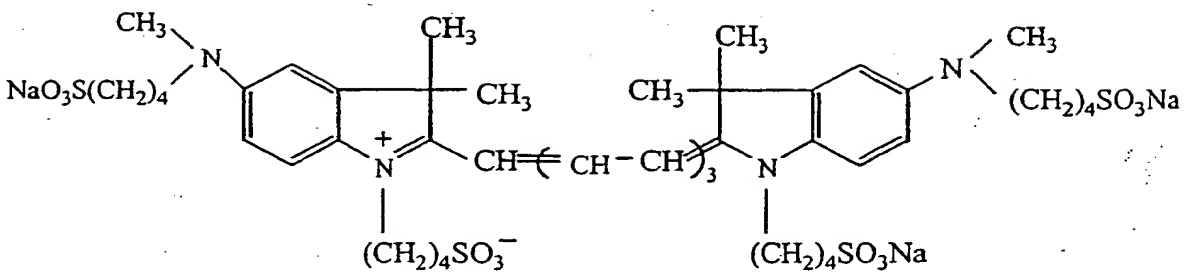


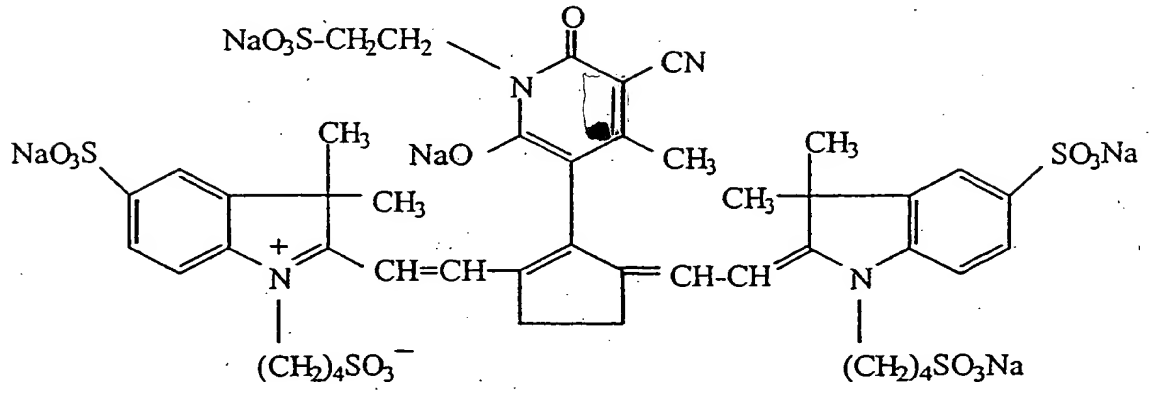


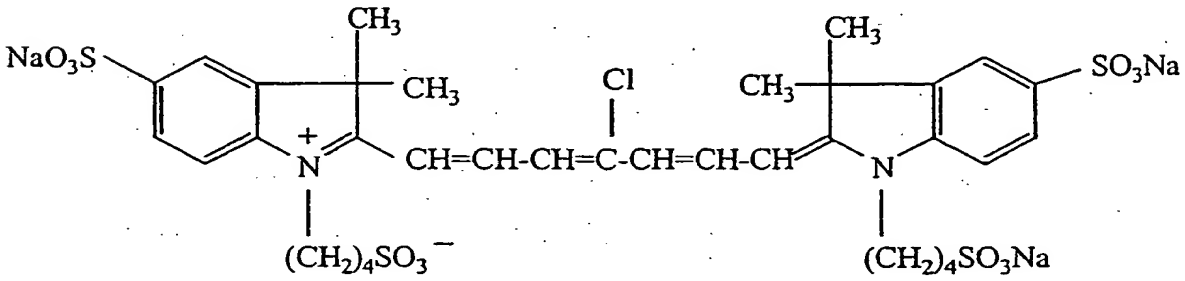


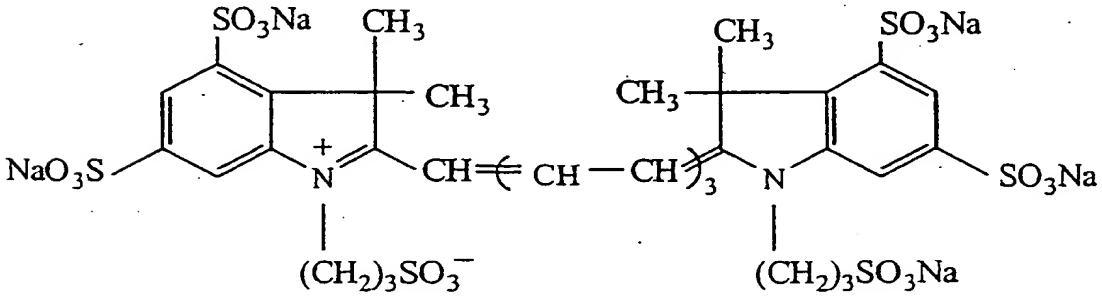


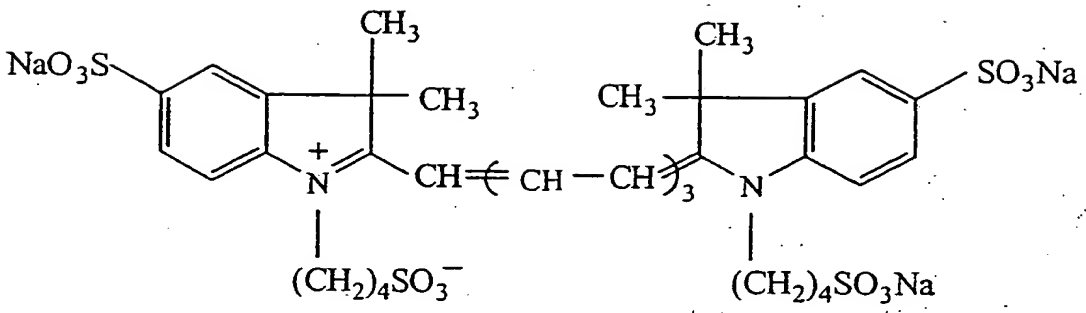


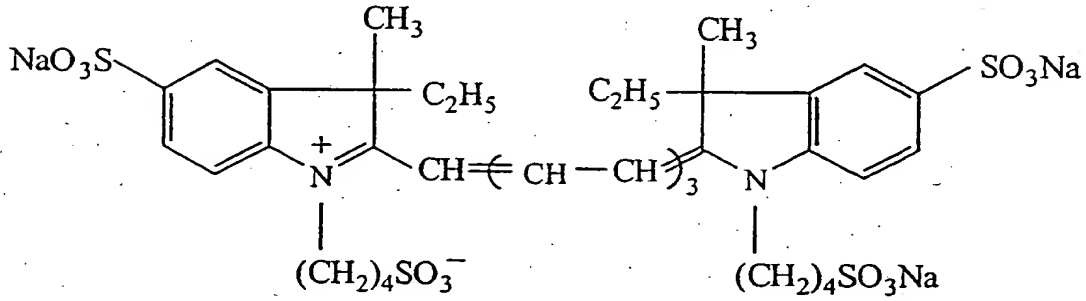


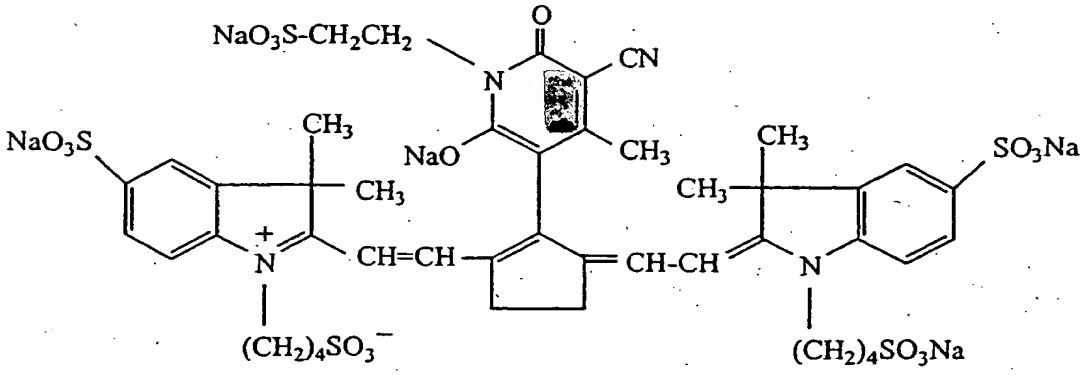


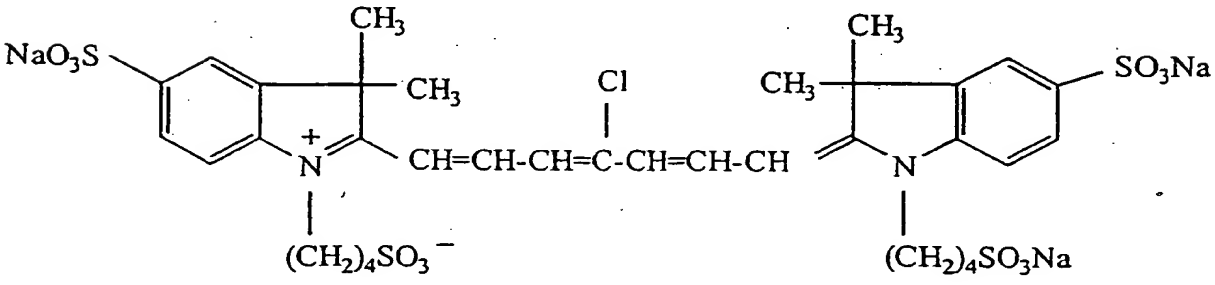












The substituent of the substituted methine group at L^8 and L^9 is exemplified by those mentioned with regard to the substituent of the above-mentioned methine groups at L^1 to L^7.

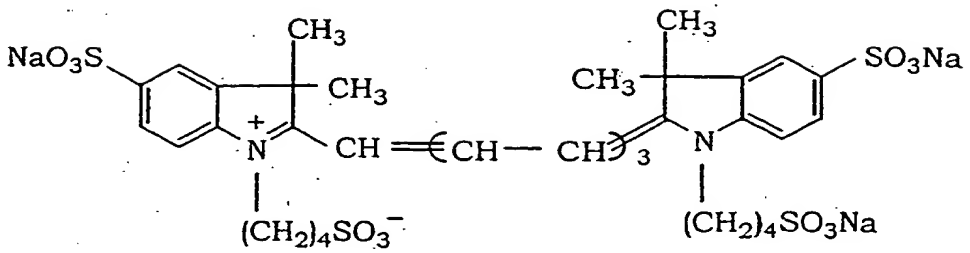
In the synthetic methods of the above-mentioned (i), (ii) and (iii), the reaction of the compounds [IV-1] and [V-1], that of the compounds [VIII-1] and [XI-1], that of the compounds [IV-1] and [V-2], that of the compounds [VIII-2] and [IX-2], that of the compounds [IV-1] and [V-3] and that of the compounds [VIII-3] and [IX-3] proceed at a temperature of –20℃ - 80℃, preferably –10℃ - 40℃, preferably in the presence of an acylating agent such as acetic anhydride.

In the synthetic methods of the above-mentioned (i), (ii) and (iii), the reaction of the compounds [IV-1] and [VII], that of the compounds [X-1] and [VII], that of the compounds [VI-2] and [VII], that of the compounds [X-2] and [VII], that of the compounds [VI-3] and [VII] and that of the compounds [X-3] and [VII] proceed at a temperature of preferably 0℃ - 40℃, preferably in the presence of a solvent such as alcohol and water.

In the synthetic methods of the above-mentioned (i), (ii) and (iii), the base to be used may be, for example, triethylamine, tributylamine, pyridine, diazabicycloundecene, sodium methoxide and the like; the solvent to be used may be, for example, an amide compound such as N,N-dimethylacetamide, N-methylpyrrolidone and N,N-diethylformamide or alcohols such as methanol; and the organic acid residue may be, for example, CH_3COO and the like.

With regard to the production of various pharmaceutically acceptable salts of the compounds of the aforementioned formula [I], ammonium salt and potassium salt of the compounds of the formula [I] can be obtained by, for example, substituting the compound of the formula [VII] used in the above-mentioned synthetic methods (i), (ii) and (iii) with a compound of the formula [VII] wherein the sodium atom has been changed to ammonium group or potassium atom; and different cationic salts of the compounds of the aforementioned formula [I] can be obtained by converting said ammonium salt and potassium salt to

(11)



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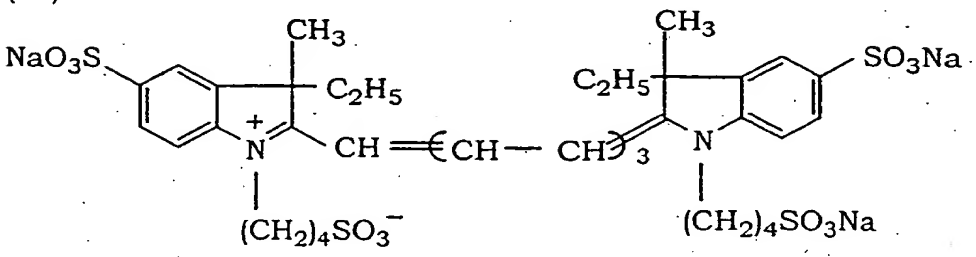

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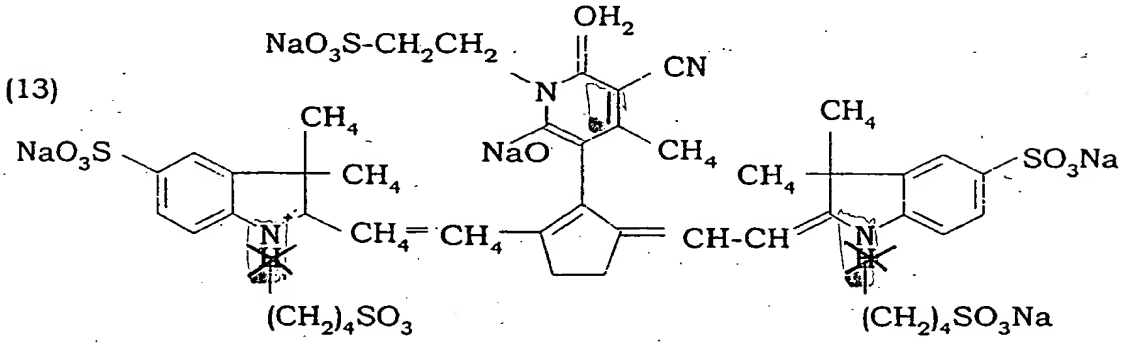

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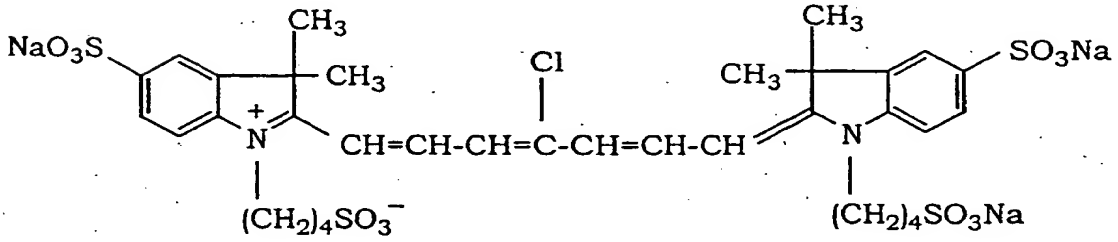

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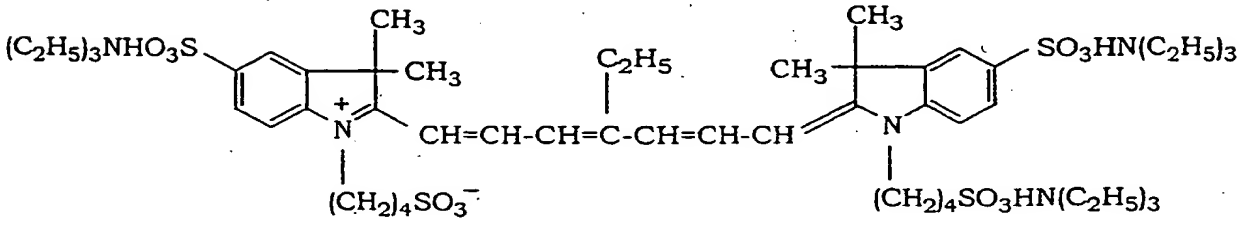

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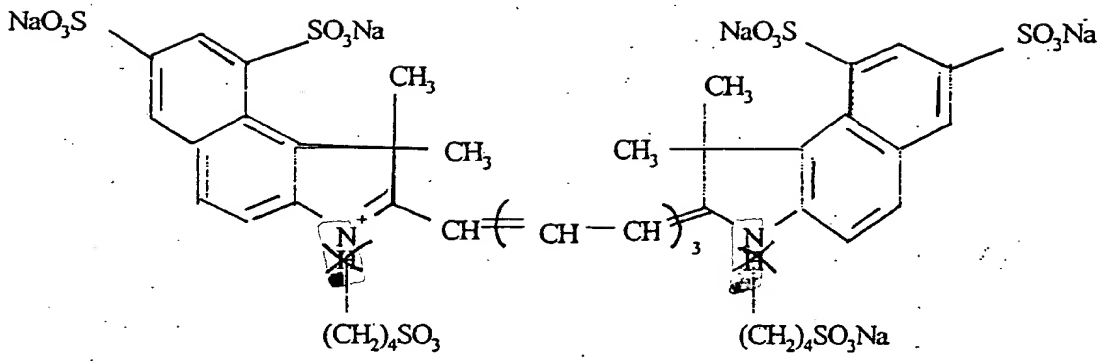

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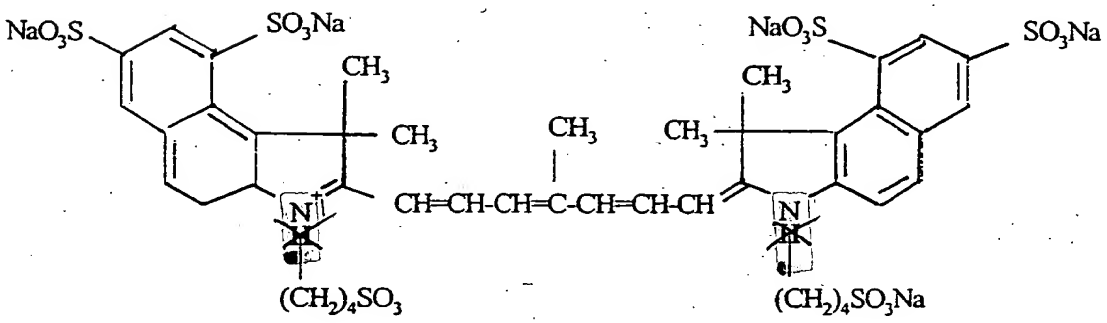

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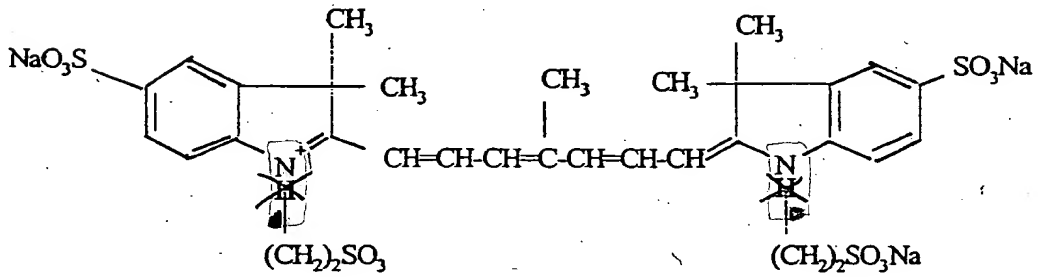

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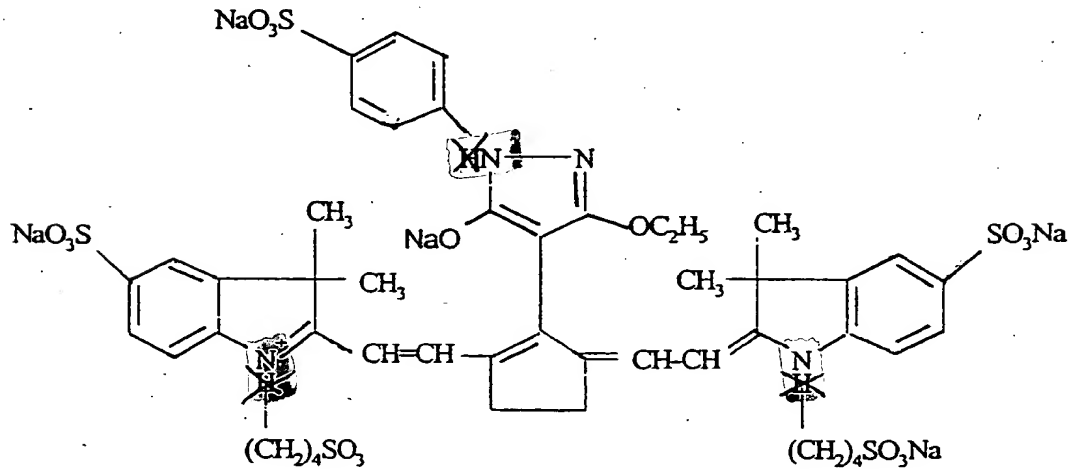


Examples

In the following Examples, the compounds are referred to with the symbols (e.g., A1, Q1 and the like) used in Tables 1 to 3 for the convenience's sake.

Example 1 : Synthesis of compound (29)

To heterocyclic quaternary salt compound Q1 (5 g) were added methanol (100 ml), N,N-dimethylformamide (25 ml), triethylamine (5.6 ml), dianyl compound A1 (1.83 g) and acetic anhydride (3 ml), and the mixture was stirred at room temperature for 4 hours. Triethyl amine (2.2 ml) and acetic anhydride (2 ml) were added, and the mixture was stirred at room temperature for 3 hours. The insoluble matter was filtered off, and a solution of sodium acetate (2 g) in methanol (15 ml) was added to the filtrate, which was followed by stirring at room temperature for 1 hour. The resulting crystals were collected by filtration and washed with a small amount of methanol. To the obtained crude crystals (3.5 g) was added water (20 ml) for dissolution. Sodium acetate (1 g) was added, and then methanol (30 ml) was added, which was followed by stirring for 1 hour. The resulting crystals were collected by filtration, washed with a small amount of methanol and dried to give 3 g of compound (29). The obtained compound (29) showed yellow in a flame test.

Maximum wavelength of absorbance (H_2O) : 780 nm

Molar absorption coefficient (H_2O) : 243,000

Maximum wavelength of fluorescence emission (H_2O) : 802 nm

The infrared absorption spectrum was measured for the obtained compound (29) by potassium bromide tablet method using a Fourier transform infrared spectrometer (VALOR-III, manufactured by JASCO). The following peaks were detected. The spectrum is shown in Fig. 11.

IR (<max(KBr)) : 1414, 1086, 1037, 995, 889 cm^{-1}

Example 2 : Synthesis of compound (34)

To heterocyclic quaternary salt compound Q2 (2.13 g) was added methanol (20 ml) and the mixture was cooled to 10°C. Thereto were added dianyl

compound A2 (0.75 g), triethylamine (4 ml) and acetic anhydride (2 ml), and the mixture was stirred for 20 minutes. Acetic anhydride (2 ml) was added, and the mixture was stirred at 10°C for 4 hours. The insoluble matter was filtered off, and a solution of sodium acetate (2 g) in a small amount of methanol was added to the filtrate. The resulting crystals were collected by filtration and washed with a small amount of methanol. To the obtained crude crystals was added water (7ml) for dissolution. Methanol (7 ml) was added to precipitate crystals. The resulting crystals were collected by filtration, washed with a small amount of methanol and dried to give 1.2 g of compound (34). The obtained compound (34) showed yellow in a flame test.

Maximum wavelength of absorbance (H_2O) : 794 nm

Molar absorption coefficient (H_2O) : 176,000

Maximum wavelength of fluorescence emission (H_2O) : 812 nm

Example 3 : Synthesis of compound (6)

To heterocyclic quaternary salt compound Q3 (9.5 g) are added methanol (50 ml), triethylamine (7 ml), dianyl compound A3 (3.1 g) and acetic anhydride (3.9 ml), and the mixture is stirred at room temperature for 7 hours. The insoluble matter is filtered off, and a solution of sodium acetate (5 g) in a small amount of methanol is added to the filtrate. The mixture is stood overnight. The resulting crystals are collected by filtration and washed with a small amount of methanol. To the crystals is added water (30 ml) for dissolution. Sodium acetate (2 g) is added, and then methanol (30 ml) is added. The resulting crystals are collected by filtration, washed with a small amount of methanol and dried to give compound (6).

Example 4 : Synthesis of compound (45)

To heterocyclic quaternary salt compound Q3 (4.8 g) were added methanol (50 ml), triethylamine (4 ml), dianyl compound A4 (1.7 g) and acetic anhydride (2 ml), and the mixture was stirred at room temperature for 3 hours. The insoluble matter was filtered off, and a solution of sodium acetate (4 g) in a small amount of methanol was added to the filtrate. The resulting crystals

Example 6 : Synthesis of compound (43)

To heterocyclic quaternary salt compound Q3 (3.75 g) were added methanol (25 ml), triethylamine (3.5 ml), dianyl compound A6 (1.95 g) and acetic anhydride (2.4 ml), and the mixture was stirred at room temperature for 1 hour. The insoluble matter was filtered off, and a solution of sodium acetate (3.9 g) in a small amount of methanol was added to the filtrate. The mixture was stirred at room temperature for 1 hour. The resulting crystals were collected by filtration and washed with a small amount of methanol. To the crystals was added water (10 ml) for dissolution. Sodium acetate (2 g) was added, and then methanol (10 ml) was added. The resulting crystals were collected by filtration, washed with a small amount of methanol and dried to give 1.8 g of compound (43). The obtained compound (43) showed yellow in a flame test.

Maximum wavelength of absorbance (H_2O) : 773 nm

Molar absorption coefficient (H_2O) : 204,000

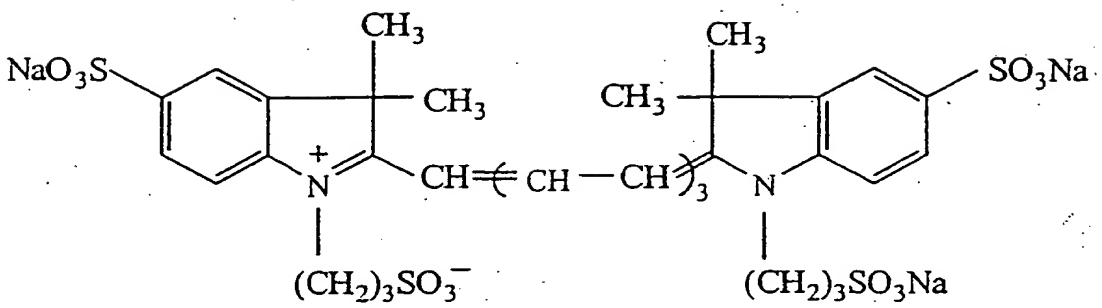
Maximum wavelength of fluorescence emission (H_2O) : 789 nm

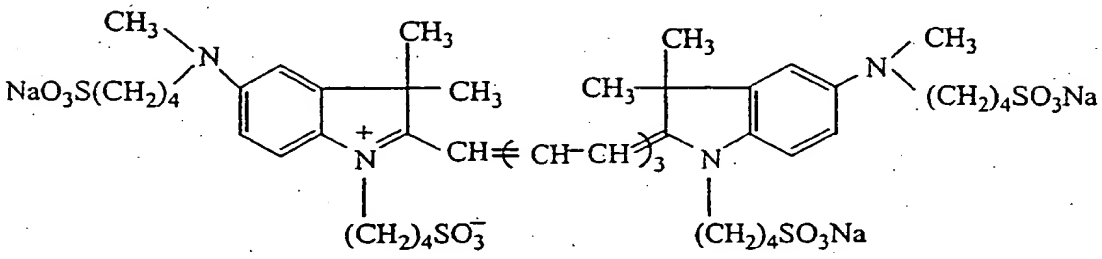
Example 7 : Synthesis of compound (4)

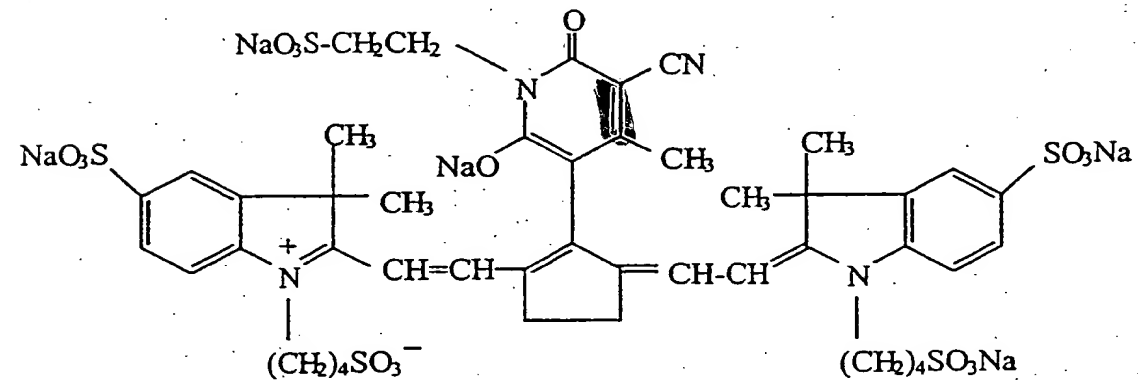
To heterocyclic quaternary salt compound Q3 (3.5 g) are added methanol (20 ml), triethylamine (3.5 ml), dianyl compound A7 (1.2 g) and acetic anhydride (1.9 ml), and the mixture is stirred at room temperature for 10 hours, and then stood overnight. The mixture is stirred under heating at 50°C for 5 hours. Water (2 ml) is added and the insoluble matter is filtered off. A solution of sodium acetate (5 g) in a small amount of water is added to the filtrate. The mixture is stirred at room temperature for 30 minutes. The resulting crystals are collected by filtration and washed with a small amount of methanol and dried to give compound (4).

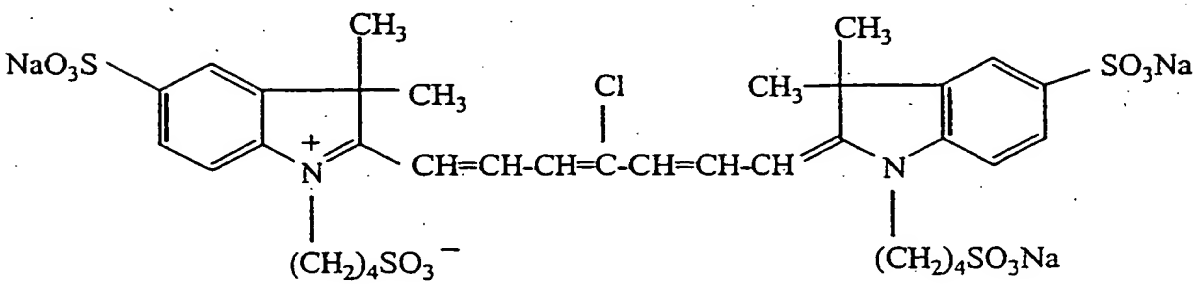
Example 8 : Synthesis of compound (31)

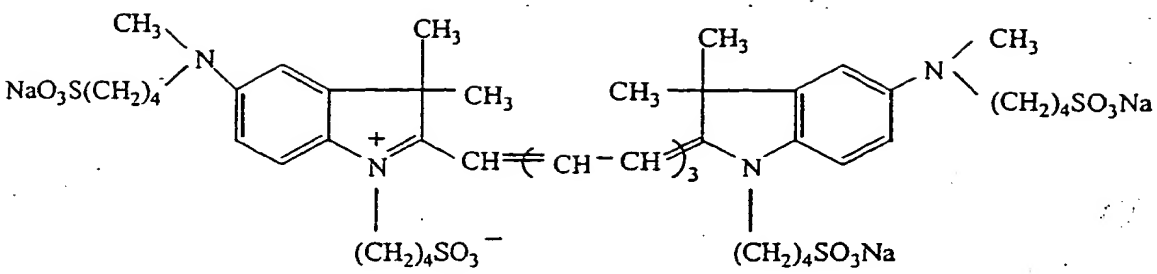
To heterocyclic quaternary salt compound Q4 (3.5 g) were added methanol (35 ml), triethylamine (3.5 ml) and acetic anhydride (2 ml), and dianyl comound A2 (1.8 g) was added portionwise with stirring. The mixture was further stirred for 1 hour. Acetic anhydride (2 ml) was added, and the mixture was stirred at

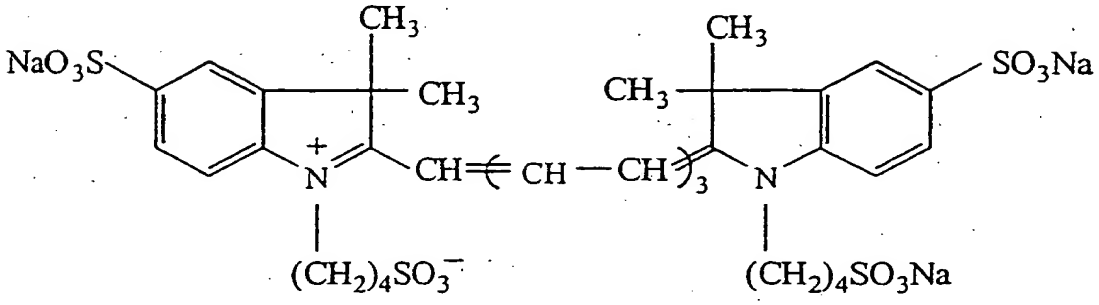


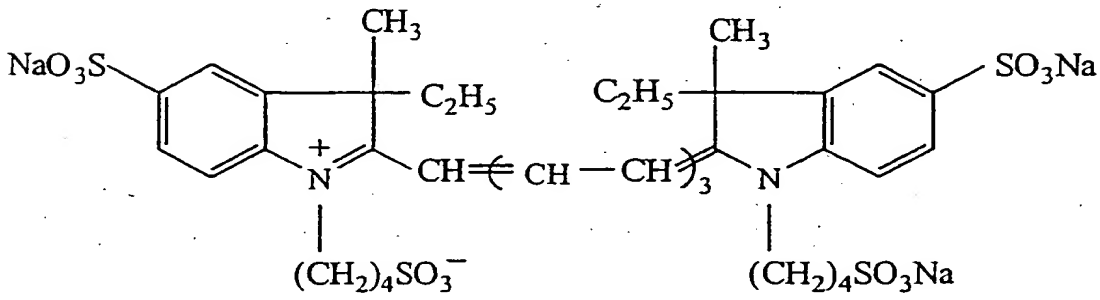


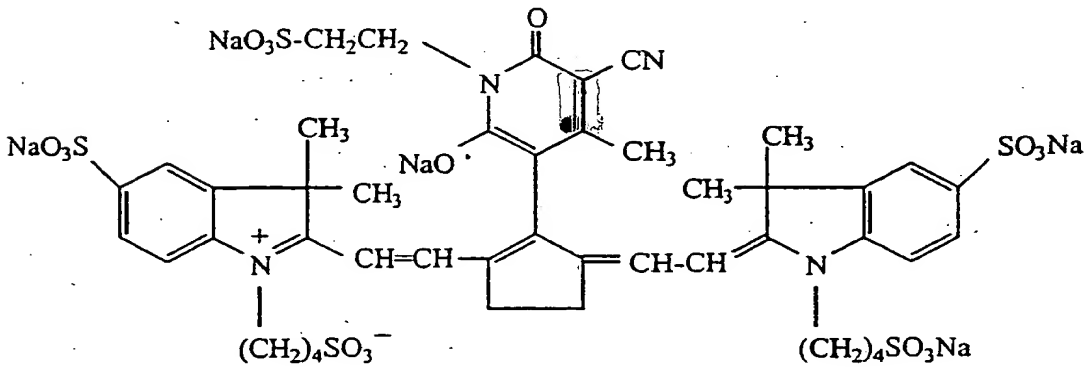


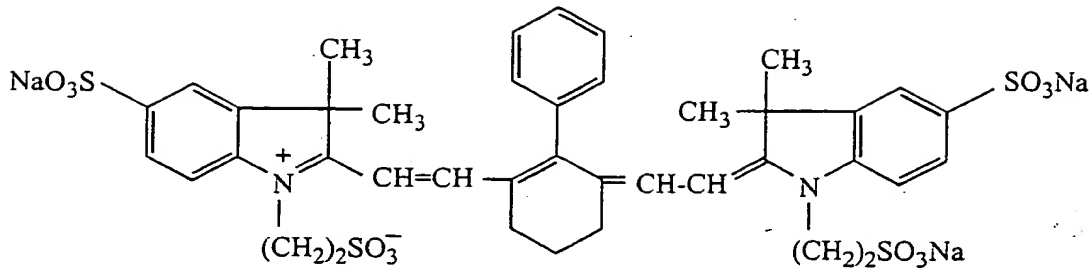


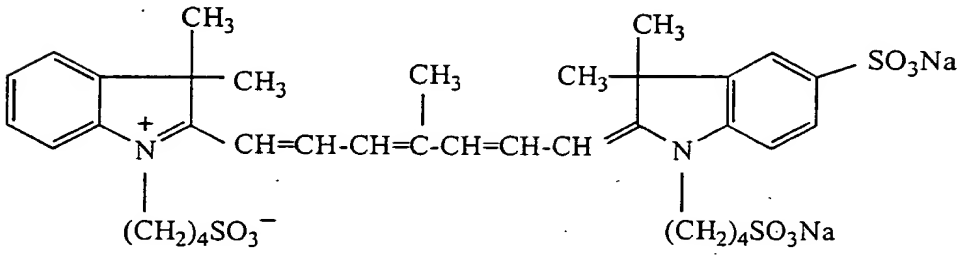


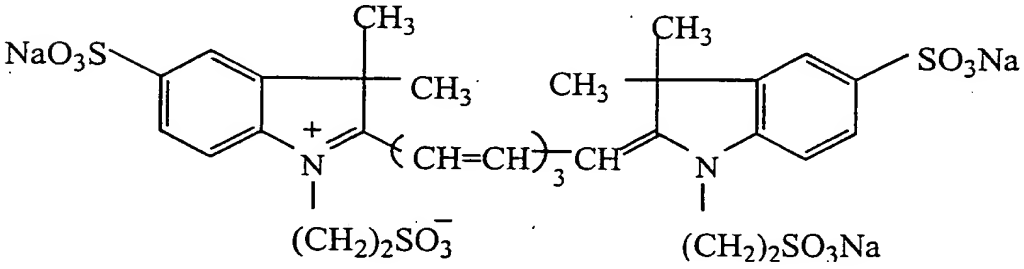


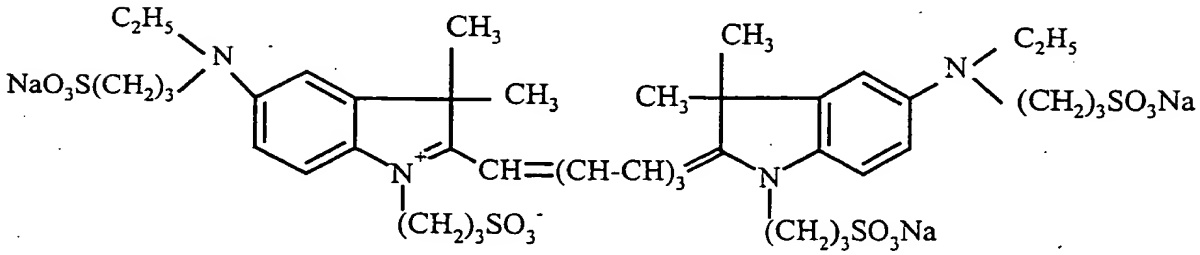


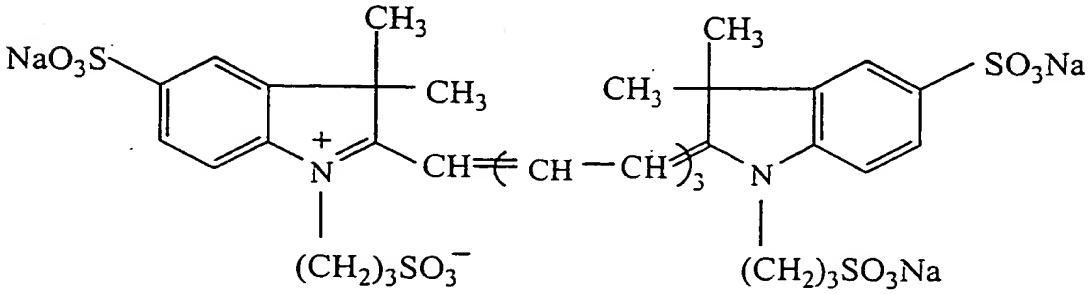


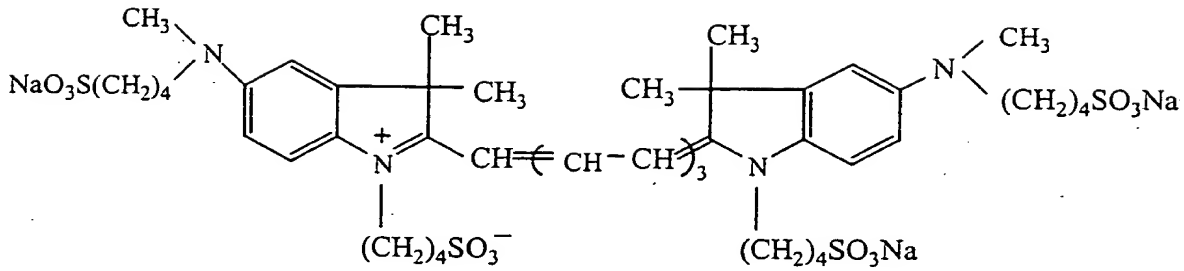


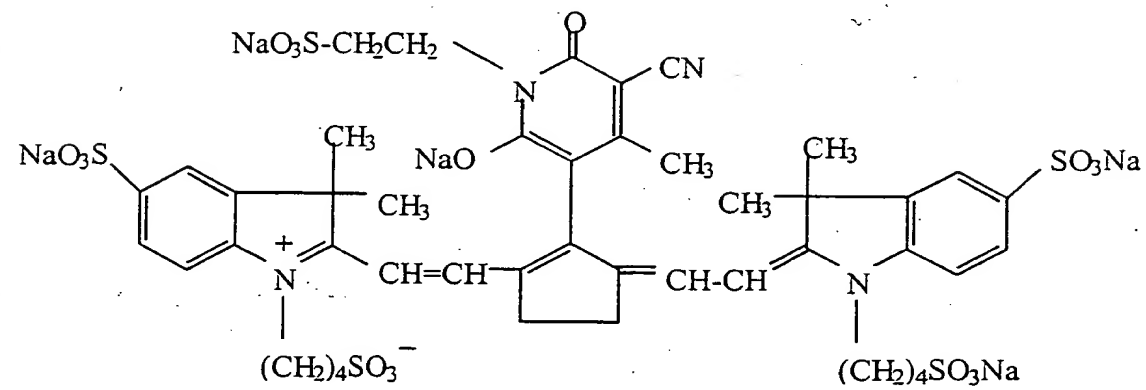


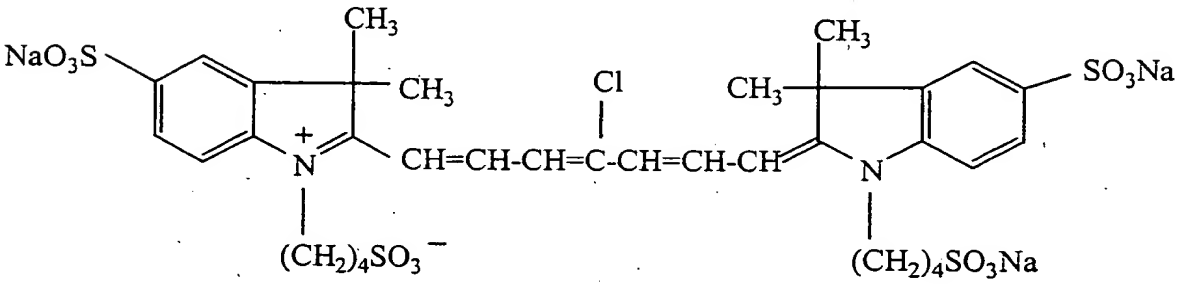


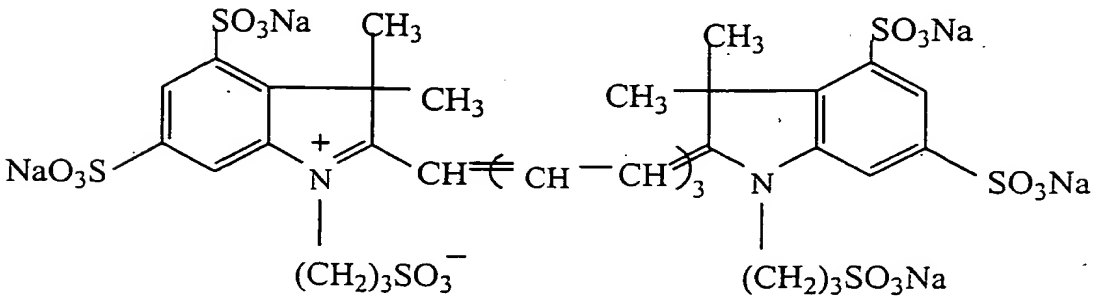


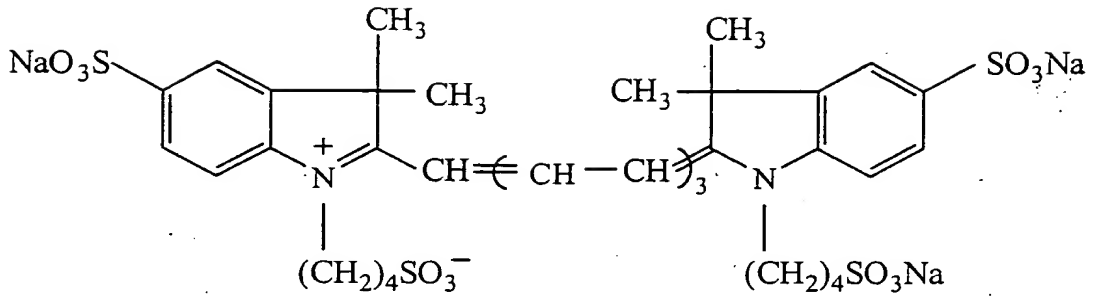


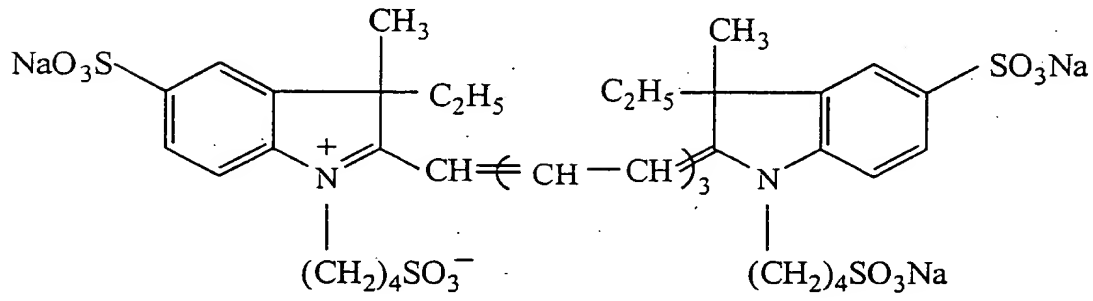


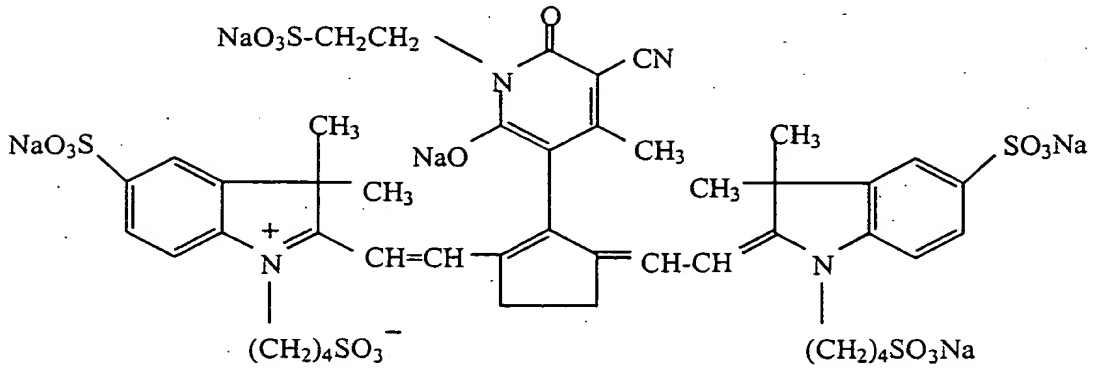


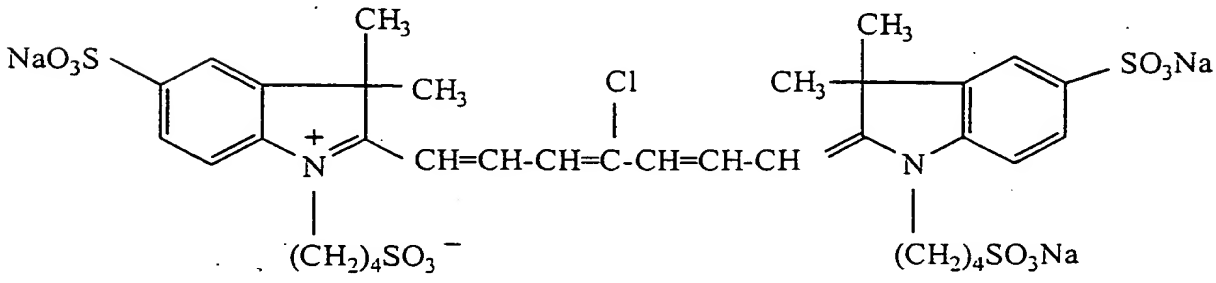












The substituent of the substituted methine group at L^8 and L^9 is exemplified by those mentioned with regard to the substituent of the above-mentioned methine groups at L^1 to L^7.

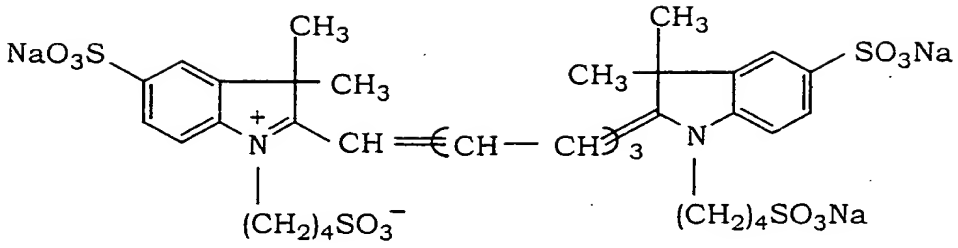
In the synthetic methods of the above-mentioned (i), (ii) and (iii), the reaction of the compounds [IV-1] and [V-1], that of the compounds [VIII-1] and [XI-1], that of the compounds [IV-1] and [V-2], that of the compounds [VIII-2] and [IX-2], that of the compounds [IV-1] and [V-3] and that of the compounds [VIII-3] and [IX-3] proceed at a temperature of –20°C – 80°C, preferably –10°C – 40°C, preferably in the presence of an acylating agent such as acetic anhydride.

In the synthetic methods of the above-mentioned (i), (ii) and (iii), the reaction of the compounds [IV-1] and [VII], that of the compounds [X-1] and [VII], that of the compounds [VI-2] and [VII], that of the compounds [X-2] and [VII], that of the compounds [VI-3] and [VII] and that of the compounds [X-3] and [VII] proceed at a temperature of preferably 0°C – 40°C, preferably in the presence of a solvent such as alcohol and water.

In the synthetic methods of the above-mentioned (i), (ii) and (iii), the base to be used may be, for example, triethylamine, tributylamine, pyridine, diazabicycloundecene, sodium methoxide and the like; the solvent to be used may be, for example, an amide compound such as N,N-dimethylacetamide, N-methylpyrrolidone and N,N-diethylformamide or alcohols such as methanol; and the organic acid residue may be, for example, CH_3COO and the like.

With regard to the production of various pharmaceutically acceptable salts of the compounds of the aforementioned formula [I], ammonium salt and potassium salt of the compounds of the formula [I] can be obtained by, for example, substituting the compound of the formula [VII] used in the above-mentioned synthetic methods (i), (ii) and (iii) with a compound of the formula [VII] wherein the sodium atom has been changed to ammonium group or potassium atom; and different cationic salts of the compounds of the aforementioned formula [I] can be obtained by converting said ammonium salt and potassium salt to

(11)



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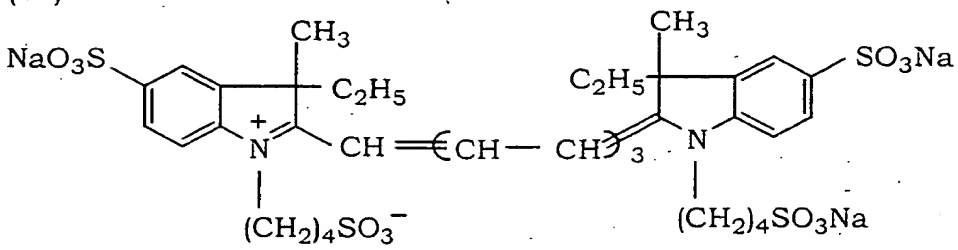

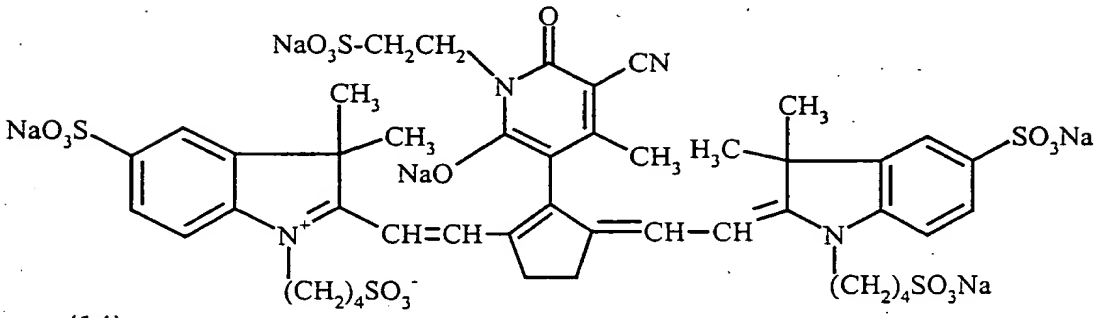

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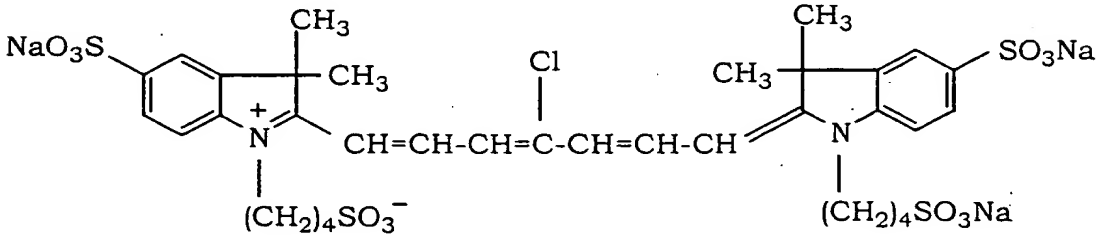

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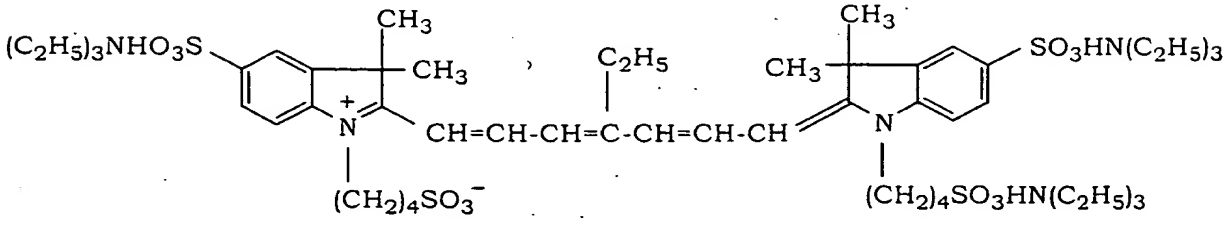

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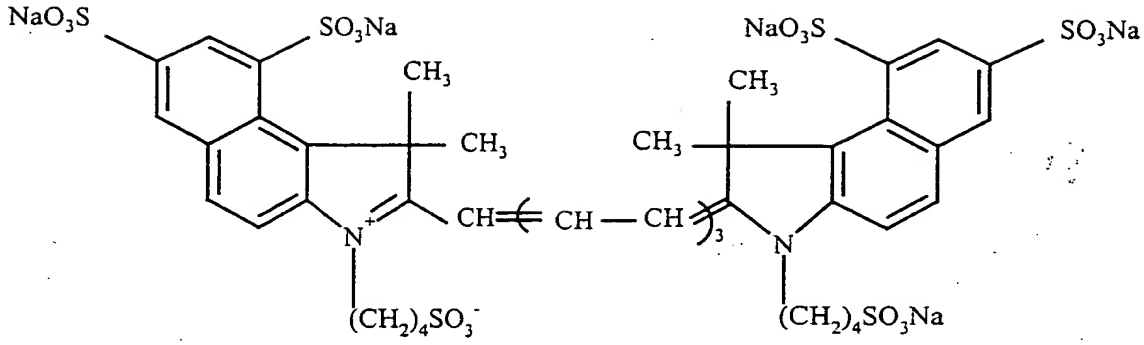

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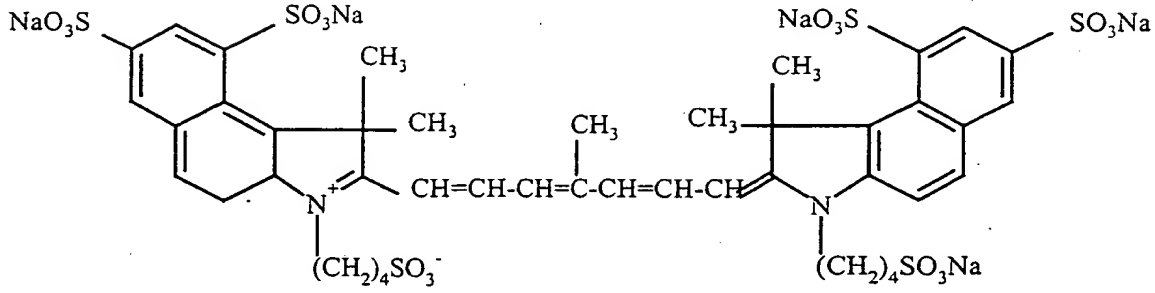

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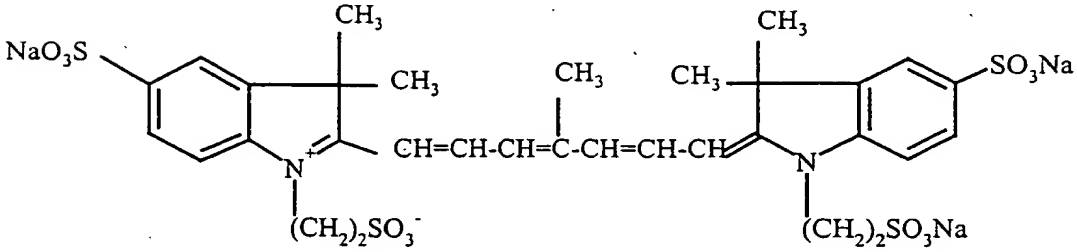

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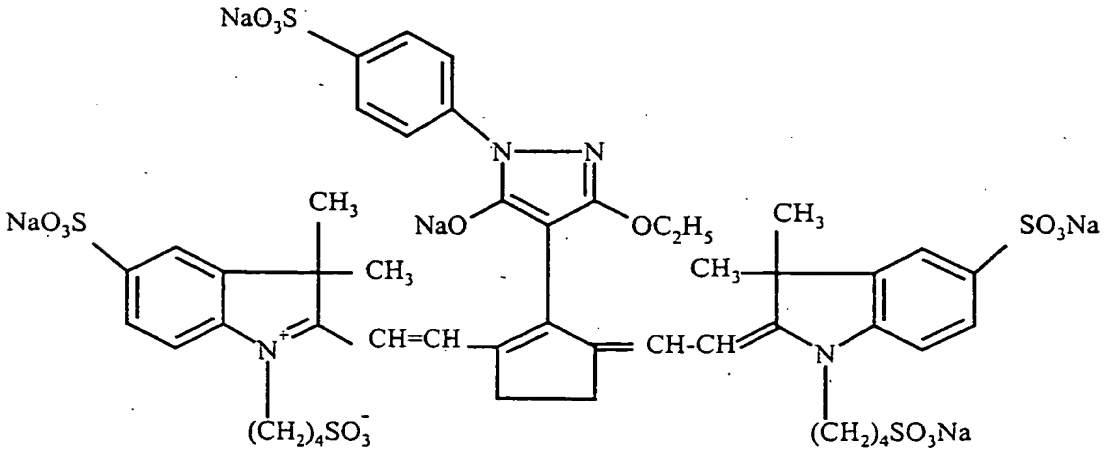

Examples

In the following Examples, the compounds are referred to with the symbols (e.g., A1, Q1 and the like) used in Tables 1 to 3 for the convenience's sake.

Example 1 : Synthesis of compound (29)

To heterocyclic quaternary salt compound Q1 (5 g) were added methanol (100 ml), N,N-dimethylformamide (25 ml), triethylamine (5.6 ml), dianyl compound A1 (1.83 g) and acetic anhydride (3 ml), and the mixture was stirred at room temperature for 4 hours. Triethyl amine (2.2 ml) and acetic anhydride (2 ml) were added, and the mixture was stirred at room temperature for 3 hours. The insoluble matter was filtered off, and a solution of sodium acetate (2 g) in methanol (15 ml) was added to the filtrate, which was followed by stirring at room temperature for 1 hour. The resulting crystals were collected by filtration and washed with a small amount of methanol. To the obtained crude crystals (3.5 g) was added water (20 ml) for dissolution. Sodium acetate (1 g) was added, and then methanol (30 ml) was added, which was followed by stirring for 1 hour. The resulting crystals were collected by filtration, washed with a small amount of methanol and dried to give 3 g of compound (29). The obtained compound (29) showed yellow in a flame test.

Maximum wavelength of absorbance (H_2O) : 780 nm

Molar absorption coefficient (H_2O) : 243,000

Maximum wavelength of fluorescence emission (H_2O) : 802 nm

The infrared absorption spectrum was measured for the obtained compound (29) by potassium bromide tablet method using a Fourier transform infrared spectrometer (VALOR-III, manufactured by JASCO). The following peaks were detected. The spectrum is shown in Fig. 11.

IR (<max(KBr)) : 1414, 1086, 1037, 995, 889 cm^{-1}

Example 2 : Synthesis of compound (34)

To heterocyclic quaternary salt compound Q2 (2.13 g) was added methanol (20 ml) and the mixture was cooled to 10°C. Thereto were added dianyl

compound A2 (0.75 g), triethylamine (4 ml) and acetic anhydride (2 ml), and the mixture was stirred for 20 minutes. Acetic anhydride (2 ml) was added, and the mixture was stirred at 10 °C for 4 hours. The insoluble matter was filtered off, and a solution of sodium acetate (2 g) in a small amount of methanol was added to the filtrate. The resulting crystals were collected by filtration and washed with a small amount of methanol. To the obtained crude crystals was added water (7ml) for dissolution. Methanol (7 ml) was added to precipitate crystals. The resulting crystals were collected by filtration, washed with a small amount of methanol and dried to give 1.2 g of compound (34). The obtained compound (34) showed yellow in a flame test.

Maximum wavelength of absorbance (H_2O) : 794 nm

Molar absorption coefficient (H_2O) : 176,000

Maximum wavelength of fluorescence emission (H_2O) : 812 nm

Example 3 : Synthesis of compound (6)

To heterocyclic quaternary salt compound Q3 (9.5 g) are added methanol (50 ml), triethylamine (7 ml), dianyl compound A3 (3.1 g) and acetic anhydride (3.9 ml), and the mixture is stirred at room temperature for 7 hours. The insoluble matter is filtered off, and a solution of sodium acetate (5 g) in a small amount of methanol is added to the filtrate. The mixture is stood overnight. The resulting crystals are collected by filtration and washed with a small amount of methanol. To the crystals is added water (30 ml) for dissolution. Sodium acetate (2 g) is added, and then methanol (30 ml) is added. The resulting crystals are collected by filtration, washed with a small amount of methanol and dried to give compound (6).

Example 4 : Synthesis of compound (45)

To heterocyclic quaternary salt compound Q3 (4.8 g) were added methanol (50 ml), triethylamine (4 ml), dianyl compound A4 (1.7 g) and acetic anhydride (2 ml), and the mixture was stirred at room temperature for 3 hours. The insoluble matter was filtered off, and a solution of sodium acetate (4 g) in a small amount of methanol was added to the filtrate. The resulting crystals

Example 6 : Synthesis of compound (43)

To heterocyclic quaternary salt compound Q3 (3.75 g) were added methanol (25 ml), triethylamine (3.5 ml), dianyl compound A6 (1.95 g) and acetic anhydride (2.4 ml), and the mixture was stirred at room temperature for 1 hour. The insoluble matter was filtered off, and a solution of sodium acetate (3.9 g) in a small amount of methanol was added to the filtrate. The mixture was stirred at room temperature for 1 hour. The resulting crystals were collected by filtration and washed with a small amount of methanol. To the crystals was added water (10 ml) for dissolution. Sodium acetate (2 g) was added, and then methanol (10 ml) was added. The resulting crystals were collected by filtration, washed with a small amount of methanol and dried to give 1.8 g of compound (43). The obtained compound (43) showed yellow in a flame test.

Maximum wavelength of absorbance (H_2O) : 773 nm

Molar absorption coefficient (H_2O) : 204,000

Maximum wavelength of fluorescence emission (H_2O) : 789 nm

Example 7 : Synthesis of compound (4)

To heterocyclic quaternary salt compound Q3 (3.5 g) are added methanol (20 ml), triethylamine (3.5 ml), dianyl compound A7 (1.2 g) and acetic anhydride (1.9 ml), and the mixture is stirred at room temperature for 10 hours, and then stood overnight. The mixture is stirred under heating at 50°C for 5 hours. Water (2 ml) is added and the insoluble matter is filtered off. A solution of sodium acetate (5 g) in a small amount of water is added to the filtrate. The mixture is stirred at room temperature for 30 minutes. The resulting crystals are collected by filtration and washed with a small amount of methanol and dried to give compound (4).

Example 8 : Synthesis of compound (31)

To heterocyclic quaternary salt compound Q4 (3.5 g) were added methanol (35 ml), triethylamine (3.5 ml) and acetic anhydride (2 ml), and dianyl comound A2 (1.8 g) was added portionwise with stirring. The mixture was further stirred for 1 hour. Acetic anhydride (2 ml) was added, and the mixture was stirred at